EFFECTS OF HIGH DOSES OF NALTREXONE ON RUNNING AND RESPONDING FOR THE OPPORTUNITY TO RUN IN RATS: A TEST OF THE OPIATE HYPOTHESIS

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Previous research shows that low to moderate doses of opiate antagonists do not affect running whereas high doses decrease running. This decrease in running has been interpreted as a motivational effect; however, it may also be an effect of motoric impairment, malaise, or sedation. The purpose of the present study was to evaluate the effects of high doses of naltrexone on running and responding for the opportunity to run in rats. Seven male Wistar rats, trained to press levers for the opportunity to run for 30 s, were exposed to a series of tandem fixed-ratio 1 variable-interval (VI) schedules of reinforcement where the value of the VI schedule was varied. Four rats were exposed to a VI 60-, VI 30-, and VI 5-s schedule order and the remaining three were exposed to VI 5-, VI 30-, and VI 60-s schedule order. After 50 sessions, doses of 10, 20, or 40 mg/kg of naltrexone were administered prior to a session. Results showed that naltrexone significantly decreased rates of lever pressing and running and increased postreinforcement latency to respond. Within-session analyses showed that naltrexone significantly decreased responding and running during the first schedule of a session regardless of schedule value. The lack of interaction of the drug effect with the schedule of reinforcement is inconsistent with a motivational effect. Consequently, it was concluded that decreases in running caused by high doses of naltrexone are not motivational and should not be taken as evidence in support of the opiate hypothesis.

After engaging in rigorous bouts of physical activity an individual sometimes experiences subjective feelings of euphoria. This phenomenon is known as “runner’s high.” Although widely known, the physiology underlying this phenomenon is not well understood. The endogenous opiate hypothesis attributes this phenomenon to a release

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of endogenous opiates that accompanies intense levels of exercise; however, evidence in support of the opiate hypothesis is not substantial (Steinberg & Sykes, 1985). For this reason further research into the pharmacological basis of the reinforcing properties of running is warranted.

Investigations into the effects of opiate antagonists on subjective reports of euphoria in long-distance runners lend tentative support to the opiate hypothesis. Janel, Colt, Clark, and Glusman (1984) found that intravenous injections of 0.8 mg/kg of naloxone attenuated post-run measures of joy and euphoria in long-distance runners. However, Markoff, Ryan, and Young (1982) found that subcutaneous injections of the same dose had no effect on elevated post-run measures of mood in long-distance runners.

Evidence from animal studies on the effects of opiate antagonists on running also does not produce an unambiguous interpretation of the role of endogenous opiates. Low to moderate doses of opiate antagonists, sufficient to antagonize hyperactivity induced by exogenous opiates (Schnur, Hang, & Stinchcomb, 1987), do not affect running (Carey, Ross, & Enns, 1981; Schnur & Barela, 1984) whereas high doses do (Boer, Epling, & Pierce, 1990; Potter, Borer, & Katz, 1983; Russell & Morse, 1996). Numerous studies have demonstrated the absence of an effect on running at low doses. For example, Carey et al. (1981) found no effects of ip injections of 1.0 and 10.0 mg/kg doses of naloxone on wheel revolutions in rats. At higher doses, opiate antagonists decrease running which is consistent with the prediction of the opiate hypothesis. For example, Potter et al. (1983) found that a 20 mg/kg dose of naltrexone significantly reduced spontaneous running in female Golden hamsters over a 12-hour period. Based on the observation that the same dose did not affect lever pressing for hypothalamic self-stimulation in a second group of animals, Potter et al. (1983) interpreted the decrease in running to be a motivational effect.

Although reductions in running produced by high doses of opiate antagonists are consistent with the opiate hypothesis, the dose range required to produce these reductions raises the possibility that the effect may be motoric, malaise-induced, or sedation-induced rather than motivational. Reductions in running due to motor, malaise, or sedation effects would not be consistent with the opiate hypothesis. The purpose of the present study was to investigate the effects of high doses of naltrexone on running and responding for the opportunity to run in an attempt to differentiate between these alternative explanations.

Method

Subjects

Selected from an initial group of 10 rats and based on running rates, 8 male Wistar rats served as subjects. The rats were individually housed in polycarbonate cages (20 x 24 x 40 cm) in a holding room on a 12-hr light/dark cycle (lights on 08:00). Subjects were maintained at 80% of their initial free-feed body weights with free access to distilled water in
the home cage. Agway Prolab RMH-3000 chow was fed to the rats in measured amounts to maintain them at their target weights.

**Apparatus**

Subjects were tested in standard activity wheels (3 Wahmann and 5 LaFayette Instruments Model #86041 A) with diameters of 35.5 cm. Wheels were located in soundproof shells equipped with fans for ventilation and to mask extraneous noise. A retractable lever (Med Associates ENV-112) was mounted at the opening of each wheel. The lever extended 1.8 cm into the chamber through an opening (7 x 9 cm) in the center at the base of the wheel frame. A microswitch attached to the wheel frame recorded wheel revolutions. The force required to close the lever microswitches ranged between 18 and 27 g. Mounted on the sides of the wheel frame, 24-V DC lights illuminated the interior of the wheel. Control of experimental events and recording of data were handled by IBM® personal computers interfaced to the wheel through the parallel port.

**Procedure**

**Training.** Initially 10 rats were given free access to a running wheel for 30 min each day for a total of 10 days. After 10 days, the 8 rats that ran at the highest rate were selected for the study. Following this phase, the selected rats were shaped to press a lever in a standard operant conditioning chamber. Each press of the lever produced 0.1 ml of .3M sucrose solution. When subjects reliably pressed the lever, the schedule of reinforcement was shifted from a continuous reinforcement schedule to a variable-ratio (VR) schedule. The subjects passed through the following series of schedules: VR3, VR5, and VR10. Each schedule was in effect for 4 days.

Subjects continued to run in wheels daily for a single 30-min session throughout the period of lever training. Following the 4th day on the VR10 schedule, lever-pressing sessions in the operant chamber were discontinued. The retractable lever in the wheel chamber was made operative and the opportunity to run for 60 s was contingent upon a single lever press. A single lever press released the brake and produced the opportunity to run for 60 s. Each session consisted of 30 reinforcements or opportunities to run. This fixed-ratio (FR) 1 schedule was in effect for 6 days.

Training the subjects to respond on a series of reinforcement schedules within the same session proceeded through the following steps. The schedule of reinforcement was successively shifted through the following sequence: VR3, VR5, VR9, and VR15. Subjects remained on each schedule for 4 days before advancing to the next schedule. One rat was dropped from the study during this training phase for failure to complete the sessions (e.g., only 10 reinforcement periods were obtained in a 2.5-hr session compared to 30 reinforcement periods by the remaining rats in less than 1.5 hr).

After the 4th day on the VR15 schedule, the session was changed to a
sequence of three tandem FR1 variable-interval (VI) schedules (i.e., VI 5, VI 30, and VI 60) and the reinforcement period was shifted from 60 to 30 s. On a tandem FR1 VI schedule, the interval for the VI schedule does not start to elapse until a response occurs. Each VI schedule was composed of 10 intervals and the order of intervals was randomized across sessions.

Within a session, successful completion of 13 reinforcers in each component on a given tandem FR1 VI schedule was followed by a 2-min blackout period during which the lights were turned off and the brake was engaged. When the blackout period expired, the lever extended, the lights were turned on, and the animal was given the opportunity to obtain another 13 reinforcers on a different reinforcement schedule. Of the 13 reinforcers in each VI component of a tandem FR1 VI schedule, the first 3 reinforcers were "warm up" reinforcers meant to diminish interactions between the tandem FR1 VI schedules. The interval values for these "warm-up" reinforcers were determined by multiplying the values 4, 5, and 6 by the multiplier that was used to produce the intervals for the remaining 10 reinforcers. Data from these "warm-up" reinforcers were not included in the analysis.

A session involved the completion of the three schedules for a total of 39 reinforcement periods. A given animal was presented with the same sequence of tandem FR1 VI schedules across all sessions; however, the sequences of VI schedule components were counterbalanced across rats. Three rats were exposed to a VI 5-, VI 30-, and VI 60-s sequence and 4 rats were exposed to a VI 60-, VI 30-, and VI 5-s sequence. After each session the animals were weighed and fed a measured amount of food to maintain them at 80% of an initial free-feed body weight.

Drug testing. After 50 sessions, drug testing commenced. Naltrexone HCL (Sigma Chemical Company, St. Louis, MO) was administered by intraperitoneal injection 15 minutes prior to a session. The vehicle was saline. Doses of 10, 20, and 40 mg/kg were given in randomized order. Each dose was administered three times. Between administrations of naltrexone, vehicle and baseline sessions occurred.

The dependent measures recorded in each session were number of wheel revolutions, cumulative postreinforcement latency, lever presses, and time spent lever pressing. Similar measures were also recorded for each reinforcement to investigate within-session drug effects. A repeated measures, one-way analysis of variance (ANOVA) was performed to test for a drug effect and post-hoc comparisons were used as a means of assessing dose effects relative to saline levels.

Results

Figure 1 depicts mean local lever-pressing rates, postreinforcement latencies, and wheel-running rates in the baseline, 0 (saline), 10, 20, and 40 mg/kg conditions in the top, middle, and bottom panels, respectively. In general, local lever-pressing rates decreased as the dose of
Figure 1. Mean local response rates (lever presses/min), mean postreinforcement latencies to lever press (s), and wheel-running rates (revolutions/min) in the baseline, 0 (saline) 10, 20, and 40 mg/kg naltrexone dose conditions are displayed in the top, middle, and bottom panels, respectively.
naltrexone increased. Mean response rates across the five conditions were 17.58, 16.13, 13.93, 12.67, and 10.51 responses/min, respectively. A repeated measures ANOVA revealed a significant effect of dose, $F(3, 18) = 6.43$, $p < .01$. Post-hoc Dunnett's $t$ tests revealed that response rates were significantly ($p < .05$) decreased by the 20, $t_{(18)} = 2.64$, and 40 mg/kg doses, $t_{(18)} = 4.23$. The middle panel shows that mean postreinforcement latencies to lever press increased with dose. Across the five conditions, mean latencies were 72.49, 81.16, 90.57, 88.24, and 101.86 s, respectively. A repeated measures ANOVA revealed a significant effect of dose, $F(3, 18) = 3.07$, $p = .05$ and Dunnett's $t$ tests revealed that only the increase in latency by the 40 mg/kg dose, $t_{(18)} = 2.99$, was statistically significant. Finally, the bottom panel shows that wheel-running rates decreased with dose. Mean wheel-running rates in the baseline, 0, 10, 20, and 40 mg/kg conditions were 32.79, 31.43, 30.41, 27.96, and 27.47 revolutions/min, respectively. A repeated measures ANOVA revealed a significant effect of dose, $F(3, 18) = 7.48$, $p < .01$. Post-hoc Dunnett's $t$ tests showed that wheel running was significantly decreased by the 20, $t_{(18)} = 3.52$, and 40 mg/kg doses, $t_{(18)} = 4.01$.

An analysis was also performed on the effect of naltrexone on response rates, postreinforcement latencies, and wheel-running rates for each schedule of reinforcement by presentation order. Figure 2 shows mean local response rates, mean postreinforcement latencies, and mean wheel-running rates as a function of the reinforcement schedule in the baseline, saline, 10 mg/kg, 20 mg/kg, and 40 mg/kg conditions. Data for rats on the VI 60- to VI 5-s schedule order are depicted in the left panel and data for the rats on the VI 5- to VI 60-s schedule order are depicted in the right panel.

Inspection of the top panels shows that for rats on both schedule orders, local response rates varied inversely with schedule value, though the effect on response rates under baseline conditions appears greater for the rats exposed to the VI 60- to VI 5-s schedule order. Second, the effect of naltrexone on response rates appears to be most evident in the first schedule of a session and least evident in the last schedule of a session. Furthermore, the effect of naltrexone on response rates in the first schedule in a session does not appear to differ depending upon the schedule of reinforcement.

To substantiate these observations, repeated measures ANOVAs with schedule value (5, 60) as a between-subject variable and dose (0, 10, 20, and 40 mg/kg) as a within-subject variable were conducted on response rates in the first and last schedules of the sessions. Table 1 reports the $F$ values from these analyses. For the first schedules, there was a significant dose effect, but no schedule effect or schedule x dose interaction. For the last schedules, both the schedule effect and the schedule x dose interaction attained significance; however, there was no effect of dose. Thus, naltrexone affected response rates in the first, but not the last schedules of a session and the effect of naltrexone on response rates in the first schedule did not differ as a function of the reinforcement schedule.
Figure 2. Mean local response rates (lever presses/min), postreinforcement latencies to lever press (s), and wheel-running rates (revolutions/min) in the baseline, 0 (saline), 10, 20, and 40 mg/kg naltrexone dose conditions as a function of reinforcement schedule within a session are displayed in the top, middle, and bottom panels, respectively. Data for the group of rats that received a VI 60-, VI 30-, and VI 5-s schedule order are depicted in the left panels and data for rats that received a VI 5-, VI 30-, and VI 60-s schedule order are depicted in the right panels.
Table 1

Table of F Values for Schedule, Dose, and Schedule x Dose Effects for Response Rates, Postreinforcement Latencies, and Wheel-Running Rates in the first and last reinforcement schedules in a session.

<table>
<thead>
<tr>
<th>Source</th>
<th>df</th>
<th>Response Rate First</th>
<th>Last</th>
<th>Latency First</th>
<th>Last</th>
<th>Wheel Running First</th>
<th>Last</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schedule</td>
<td>1</td>
<td>0.03</td>
<td>63.00**</td>
<td>3.14</td>
<td>2.45</td>
<td>1.46</td>
<td>0.43</td>
</tr>
<tr>
<td>Error</td>
<td>5</td>
<td>(146.1)</td>
<td>(82.9)</td>
<td>(30042.1)</td>
<td>(1033.1)</td>
<td>(63.1)</td>
<td>(73.0)</td>
</tr>
<tr>
<td>Dose</td>
<td>3</td>
<td>6.10**</td>
<td>2.42</td>
<td>1.89</td>
<td>1.52</td>
<td>6.68**</td>
<td>0.44</td>
</tr>
<tr>
<td>Dose x Schedule</td>
<td>3</td>
<td>0.76</td>
<td>3.96*</td>
<td>0.32</td>
<td>1.47</td>
<td>0.26</td>
<td>0.37</td>
</tr>
<tr>
<td>Error</td>
<td>15</td>
<td>(9.9)</td>
<td>(15.6)</td>
<td>(1169.6)</td>
<td>(137.71)</td>
<td>(3.1)</td>
<td>(1.5)</td>
</tr>
</tbody>
</table>

Note. *p < .05; **p < .01.

Similar patterns appear in the data for postreinforcement latencies and wheel-running rates in the middle and bottom panels, respectively. As was the case with local response rates, an increase in mean latencies is evident in the first schedules for both groups, but not apparent in the last schedules. However, the increase in latency under the influence of naltrexone failed to attain significance. For latencies, none of the effects were significant for the first or last schedules. Wheel-running rates depicted in the bottom panels also showed an effect of naltrexone in the first, but not the last schedules of a session. For both groups, naltrexone decreases wheel-running rates in the first schedule of a session. Table 1 reveals that for the first schedules, there was a significant effect of dose, but no schedule or dose x schedule interaction. For the last schedules, no significant effects occurred.

Discussion

At the session level, the results of the present study were consistent with previous studies that found that high doses of opiate antagonists decrease running. In addition to the decline in running, responding for the opportunity to run was also affected. Response rates were decreased and latencies to respond were increased by the high dose of naltrexone. Although the decline in running and changes in responding for the opportunity to run were consistent with the interpretation that naltrexone decreased motivation to run, the data at this level do not distinguish this explanation from a malaise, motor, or sedation effect.

The within-session analysis of the pattern of changes in response rates provides information that helps discriminate the nature of this effect. A matching law (Herrnstein, 1970) analysis of the drug effect
evaluates changes in the functions relating response rates to reinforcement rates. According to this analysis, an increase in motivation is characterized by response rates rising more rapidly toward an asymptotic response rate as reinforcement rate increases and a decrease in motivation is characterized by response rates rising more slowly toward the same asymptote as the reinforcement rate increases. Changes in the value of the response-rate asymptote, however, represent changes in motoric aspects of responding that do not depend on the rate of reinforcement. In summary, motivational effects of drugs vary as a function of the reinforcement rate. Response rates generated by low rates of reinforcement are affected more than response rates generated by high rates of reinforcement (e.g., see Heyman, 1992). Motoric effects of drugs do not vary with the schedule of reinforcement in this manner.

According to this description, the results from the group exposed to the VI 60- to VI 5-s order would appear consistent with a motivational interpretation. That is, the effect of naltrexone on response rates appears to diminish as the rate of reinforcement increases. However, the effect of naltrexone on the response rates of rats exposed to the VI 5- to VI 60-s order reveals that this effect does not vary as a function of reinforcement rate, but is, instead, time dependent. For this group, the effect of naltrexone on response rates appears to diminish as the rate of reinforcement decreases. Consequently, a motivational interpretation of the drug effect is not warranted. Instead, high doses of naltrexone produce a short term decrease in behavior, both lever pressing and running, at the beginning of a session that does not vary as a function of the schedule of reinforcement that is in effect and is considerably shorter in duration than the half-life of naltrexone (i.e., 10 hours).

In sum, decreases in running under the influence of high doses of opiate antagonists have been interpreted as evidence consistent with the hypothesis that endogenous opiates play a role in the pharmacological basis of the reinforcing effects of running. The results of the present study replicate these earlier findings; however, analysis of the drug effects within a session suggest that a motivational interpretation is not warranted. Instead, it is likely that the effect is due to a factor other than motivation such as motoric impairment, malaise, or sedation.

References


